HED DOC. NO. 014261

DATE: 08/01/00

MEMORANDUM

SUBJECT: **DICLOFOP-METHYL** - 3rd Report of the Hazard Identification Assessment Review Committee.

FROM: Robert F. Fricke, Ph.D.
Reregistration Branch II
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

and

Beth Doyle, Co-Chairman,
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Christina Jarvis, Risk Assessor
Reregistration Branch II
Health Effects Division (7509C)

PC Code: 110902

The Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of diclofop-methyl on December 7, 1999 (HED Doc No. 013899) to established acute and chronic Reference Doses (RfD) and selected the toxicological endpoints for acute and chronic dietary and occupational (dermal and inhalation) exposure risk assessments. This report was subsequently revised (HED Doc. No. 014016) to clarify the procedure for using route-to-route extrapolation for determination of short- and intermediate-term inhalation exposure.

At the December 7, 1999 meeting, the HJIARC recommended the use of the oral NOAEL of 0.23 mg/kg/day from a chronic feeding study in the rat. In a rebuttal (June 30, 2000), Aventis CropScience USA contested the selection of a chronic NOAEL for use is short- and intermediat-term inhalation exposure. that this study is inappropriate for assessment of short- and intermediate-term inhalation exposure and recommended that a subchronic feeding study in the rat be used , since the duration of this study (90 days) is more representative of the actual length of exposure.

On July 25, 2000 the HIARC considered the merit of the Registrant's proposed use of thea 90-day feeding study in the rat in establishing the endpoints for short- and intermediate-term inhalation exposure. The Committee concurred with the Registrant's proposal. The Committee's conclusions of this and previous meetings are presented in this report.

Committee Members in Attendance: Bill Burnam, David Nixon, Pam Hurley, Tina Levine, Elizabeth Mendez, Jess Rowland, Yung Yang, Jonathan Chen, Ayaad Assaad, and Brenda Tarplee.

Committee Members not in Attendance: Elizabeth Doyle

Other staff present at the meeting were C. Jarvis and P. Wagner, RRB2.

Data Presentation
and
Report Presentation: Robert F. Fricke, Ph.D., Toxicologist
Reregistration Branch 2

I. INTRODUCTION

The Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of diclofop-methyl on December 7, 1999 (HED Doc No. 013899) to established acute and chronic Reference Doses (RfD) and selected the toxicological endpoints for acute and chronic dietary and occupational (dermal and inhalation) exposure risk assessments. This report was subsequently revised (HED Doc. No. 014016) to clarify the procedure for using route-to-route extrapolation for determination of short- and intermediate-term inhalation exposure.

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II. HAZARD IDENTIFICATION

A.1 Acute Reference Dose [Population Subgroup = Females 13-50]

Study Selected: Developmental Toxicity Study - Rat 870.3700, §83-3(a)

MRID. Nos. 92036042 and 42143402

EXECUTIVE SUMMARY: In a developmental toxicity study (92036042 and 42143402 historical control data), pregnant Wistar rats (20 to 25/dose) were dosed with diclofop-methyl (96%) at 0 (vehicle, sesame oil), 10, 32, or 100 mg/kg/day from gestation day (GD) 6 through 15.

Twelve of the 20 high-dose animals died between days 13 and 21 of pregnancy. Prior to death these animals were emaciated, had blood crusts on the nasal orifice, and were hypoactive. Remaining high-dose animals and those of the other treatment groups were not impaired. At terminal sacrifice, body weight of surviving high-dose dams was 20% lower than the control value; statistically, but biologically (5%), significant decreases in body weight were noted in the mid-dose group. At the low-, mid- and high-dose levels, absolute liver weights were significantly increased (all greater than the historical control range) by 11.6%, 9.8%, and 23.1%, respectively, and relative liver weights, by 13%, 15%, and 48%, respectively. Because the liver is a target organ of toxicity, the effects on liver weights at the low-dose were considered treatment-related.

Due to the high mortality in the high-dose group, only 19 viable fetuses were available at terminal sacrifice. The number of live fetuses of the remaining low- (240) and mid- (194) were comparable to the control value (218). Fetal body weights were significantly decreased by 12.5% and 34% at the mid- and high-dose levels, respectively, and crown/rump were deceased in length by 5.8% and 18% at the mid- and high-dose levels, respectively.

With the exception of the intercurrent deaths in the high-dose group, all gestation and caesarean section parameters of treated animals were all comparable to controls. Fetal examinations revealed four major malformations in four different litters: one in the control (anophthalmia) and three in the mid-dose group (one each microphthalmia, bent hind limb, and diaphragmatic hernia). External findings consisted of increased fetal (litter) percentage of small fetuses at the mid- [6.9% (33%)] and high- [100% (100%)] dose groups. Visceral and skeletal abnormalities were evaluated by necropsy and body cross section examinations. At necropsy, visceral abnormalities consisted of increased percentages of enlarged and blood-filled heart [60% (33%)] at the high-dose level. Body cross section examination included the above abnormalities and the addition of increased percentage of distended ureter in the mid- [7.6% (28%)] and high- [22 % (33%)] dose groups. Skeletal abnormalities for fetuses (litters) at the mid- and high-dose groups included fragmented thoracic centra [5.9% (27%) and 50% (100%), respectively], weakly/non-ossified sternebrae [69% (94%) and 100% (100%), respectively] and non-ossified 5th metacarpal [62% (94%) and 100% (100%), respectively]. Although the incidence of non-ossified 5th metacarpal was increased in the low-dose group, the value was within the historical control range. At the high-dose slight/non-ossified skull bones [100% (100%)], weakly/non-ossified sacral vertebrae [40% (67%)] and pelvic girdle [20% (67%)], and non-ossified 1st - 5th toes [60% (100%)] were also observed.

Based on the results of the study (increased absolute and relative liver weights), the LOAEL for maternal systemic toxicity was established at 10 mg/kg/day, the NOAEL was not established.

Based on the results of this study (significant decreases in fetal body weight and crown-rump length, distended ureters, and skeletal abnormalities), the LOAEL for developmental toxicity was established at 32 mg/kg/day, the NOAEL was established at 10 mg/kg/day.

This study is **ACCEPTABLE-GUIDELINE**, and satisfies requirements [870.3700, §83-3(a)] for a reproductive toxicity study in the rat.

Dose and Endpoint for Establishing Acute RfD: Developmental NOAEL = 10 mg/kg/day based on significant decreases in fetal body weight and crown-rump length, distended ureters, and skeletal abnormalities at the LOAEL (32 mg/kg/day).

Comments about Study and Endpoint: This study and endpoint are considered appropriate since it is assumed that the fetal effect(s) could have resulted from a single exposure *in utero* and therefore appropriate for this population sub-group.

$$\textbf{Acute RfD (Females 13 - 50)} = \frac{\textbf{10 mg / kg / day (NOAEL)}}{\textbf{100 (UF)}} = \textbf{0.1 mg / kg / day}$$

A.2 Acute RfD [General Population including Infants and Children]

Study Selected: None

MRID. Nos.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: No appropriate endpoint was identified for this population group because there were no effects observed in oral toxicology studies including maternal toxicity in the developmental toxicity studies in rats and rabbits that are attributable to a single exposure [dose].

B. Chronic Dietary Reference Dose (RfD)

Study Selected: Combined Chronic Feeding/Carcinogenicity - rat 870.4300, §83-5

MRID. Nos.: 43927302

Executive Summary: In a chronic toxicity/oncogenicity study, diclofop-methyl was administered to a total of 80 Wistar rats/sex/dose in the diet at dose levels of 0, 4.5, 45, or 450 ppm (0, 0.23, 2.3, or 25 mg/kg body weight/day for males, and 0, 0.3, 3, or 32 mg/kg/day for females) for up to 2 years. Ten rats/sex/dose were sacrificed after 12 months. Twenty rats/sex/dose were treated in a 24-month toxicity study and 50 rats/sex/dose comprised a 24-month carcinogenicity study. Fifty additional female rats were administered the compound at 900 ppm (79 mg/kg body weight/day) for 24 weeks.

Dose levels up to 450 ppm did not increase mortality over controls. The 900 ppm dose was not tolerated by the females tested and this dose group was terminated after 24 weeks. At 45 ppm, males and females in the 24-month studies showed signs of liver toxicity, including increased liver weights, impaired lipid and protein metabolism, and increased liver enzyme activity. Related microscopic findings were hepatocellular hypertrophy, epithelial lipofuscin storage, and necrosis; the effects were more pronounced

in males. Liver cell enlargement was observed in both sexes at 45 ppm in the 12-month study. Spleen weight was decreased at 450 ppm. Increases in kidney weight in males were significant and dose-related at 45 ppm. Also at 45 ppm, kidneys of both sexes exhibited a shift in lipofuscin storage from focal to diffuse. At the high dose of 450 ppm, body weight gain was significantly reduced in both sexes in the 12-month and two 24-month studies. In the 24-month studies, treatment-related increases in absolute and/or relative liver and kidney weights were observed at the high dose in males and females. The high dose caused significant decreases in red blood cell parameters, impaired lipid and protein metabolism, and increased liver enzyme activity, more so in males than in females. In addition to the microscopic liver abnormalities seen from the 45 ppm dose, the high dose produced a significant showing of atypical eosinophilic foci and basophilic foci in both sexes.

The LOAEL for systemic toxicity is 45 ppm in male (2.32 mg/kg/day) and female (3.05 mg/kg/day) rats, based on liver toxicity manifested as increased organ weight, impaired lipid and protein metabolism, increased enzyme activity, hepatocellular hypertrophy, and increased epithelial lipofuscin storage, and increased kidney weight and a shift from focal to diffuse lipofuscin storage pattern. The NOAEL is 4.5 ppm in males (0.23-0.27 mg/kg/day) and females (0.3 mg/kg/day). The low dose of 4.5 ppm was adequate to establish a NOAEL.

The high dose of 450 ppm was adequate to assess the chronic toxicity and carcinogenic potential of diclofop-methyl in male and female rats.

Under conditions of this study, diclofop-methyl induced liver tumors in males and females, adrenal gland and testicular tumors in males, and uterine and thyroid tumors in females at 450 ppm (25.2 - 29.3 mg/kg/day, males; 32.4 - 36.6 mg/kg/day, females). The incidence of combined hepatocellular adenomas and carcinomas in the two 24-month studies was 42.0% in males and 27.1% in females. Incidence of the carcinoma, detected in 26% of males and 20% of females was higher than for the adenoma, indicating malignancy. These liver neoplasms were also observed in females at 45 ppm. In addition at 450 ppm, females exhibited a significant 8% increase in incidence of thyroid follicular cell adenoma. Incidences of uterine glandular polyps (8%), testis Leydig cell tumors (26% versus 6 and 8% in concurrent and historical controls), and adrenal gland medullary adenomas (6%) in males, also showed significant trends, and were higher than the average historical controls for the performing laboratory.

This study is classified as **ACCEPTABLE (GUIDELINE)** and satisfies the guideline requirements 83-1 for a chronic toxicity study and 83-2 for a carcinogenicity study in the rat.

Dose and Endpoint for Establishing Chronic RfD: NOAEL = 0.23 mg/kg/day. Based on increased absolute and relative liver and kidney wts, increased ALT, AST and AlkP activities, impaired lipid and protein metabolism, histopathology (hypertrophy lipofuscin storage) in males and females at 2.3 mg/kg/day (LOAEL). The NOAEL is supported by similar NOAELs and toxic effects in a carcinogenicity study in the mouse (NOAEL = 0.24

mg/kg/day).

Comments about Study and Endpoint: The endpoint of this study (liver toxicity) is consistent with other studies in both rats and mice.

Uncertainty Factor (UF): 100 (10x for inter-species extrapolation and 10x for intra-species variation).

$$\textbf{Chronic RfD} = \frac{\textbf{0.23 mg / kg / day (NOAEL)}}{\textbf{100 (UF)}} = \textbf{0.0023mg / kg / day}$$

C. Proposed Occupational/Residential Exposure

1. Dermal Absorption

Dermal Absorption Factor: 15% dermal absorption

The dermal absorption study, two formulations of diclofop-methyl (Hoelon 3EW and 3 EC) was measured in rats (42364601). The two formulations were evaluated at doses of 0.01, 0.1, and 1.0 mg/cm^2 for durations of 0.5, 1, 2, 4, 10, and 24 hours of exposure.

The percent absorption of the formulations showed a dose-related increase over time and ranged from 2 to 22% for the 3 EW and 3 to 29% for the 3 EC. The amount of material remaining on the skin was greater for the 3 EW than for the 3 EC.

Based on the results of this study, a dermal absorption factor (after 10 hours of exposure) of 15% will be used to convert oral to equivalent dermal doses.

Percent Dermal Absorption of Two Hoelon Formulations in Rats

Exposure Time (hours)	Dose (mg/cm^2)					
	Hoelon 3 EW			Hoelon 3 EC		
	0.01	0.1	1.0	0.01	0.1	1.0
0.5	2.56	3.14	4.35	3.28	6.04	7.00
1	2.48	3.00	5.71	3.33	7.01	8.23
2	3.21	6.19	2.78	2.31	7.39	6.86
4	10.03	6.77	4.78	8.03	7.28	9.58
10	9.05	14.75	7.78	7.06	15.46	8.82
24	22.14	18.38	10.95	29.16	23.02	14.67

2. Short-Term Dermal - (1-7 days)

Study Selected: 21-Day Dermal Toxicity Study in Rats 870.3200, §82-2

MRID No. 41476004

Executive Summary: In a repeated-dose dermal toxicity study, diclofop-methyl (94.5% a.i.) was applied to the clipped intact skin of 11 Wistar rats/sex/dose at nominal dose levels of 0 (diluent-treated control), 5, or 125 mg/kg/day (<limit dose), and to the clipped intact skin of six Wistar rats/sex/dose at a nominal dose level of 25 mg/kg/day for 6 hours/day, 5 days/week, for a total of 21 applications during a 30-day period. Five rats/sex in the control, 25, and 125 mg/kg/day groups were maintained for a 4-week recovery period to determine the reversibility of effects.

All animals survived the 30-day study. No treatment-related signs of dermal toxicity were observed.

No treatment-related differences in body weights, food consumption, urinalysis, or gross pathology were observed between the control and treated groups, and no neoplastic tissue was observed.

Systemic toxicity were observed in animals dosed at 25 and 125 mg/kg/day. At 25 mg/kg/day, absolute and relative liver weights were increased (males, each 35%; females, 20-21%; $p \leq 0.05$) when compared to concurrent controls. Males displayed dose-dependent increases ($p \leq 0.05$) in mean alkaline phosphatase activity (32%) and $gamma_1$-globulins (8%) and females displayed a dose-dependent increase in $alpha_1$-globulin levels (21%; $p \leq 0.05$). At 125 mg/kg/day, the liver and lipid metabolism were adversely affected. Enlarged (not tested for statistical significance) centrilobular hepatocytes were observed in 5/11 males and 3/11 females vs 0/22 controls (mean enlargement, 20.3% in males; 45.4% in females) and remained enlarged (20%) in females at the end of the recovery period. Absolute and relative liver weights were increased ($p \leq 0.05$) in males (53% and 60%, respectively) and females (57% and 48%, respectively) at the end of the treatment period and remained higher in the females (14-17%; $p \leq 0.05$) following the recovery period. Males displayed ($p \leq 0.05$) increased mean alkaline phosphatase activity (42%) and decreased cholesterol levels (30%) and females exhibited ($p \leq 0.05$) a prolonged activated partial thromboplastin time (299%) and increased levels of triglycerides (43%), total protein (12%), and $alpha_1$-globulin (22%).

Dose and Endpoint for Risk Assessment: NOAEL = 5 mg/kg/day, based on increased alkaline phosphatase activities, proteins, and absolute and relative liver weights at 25 mg/kg/day (LOAEL).

Comments about Study and Endpoint: The study and route of administration are appropriate for this endpoint.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: 21-Day Dermal Toxicity Study in Rats 870.3200, §82-2

MRID No. 41476004

Executive Summary: See Short-Term Dermal

Dose and Endpoint for Risk Assessment: See Short-Term Dermal

Comments about Study and Endpoint: See Short-Term Dermal

4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: None

MRID. Nos.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: The use pattern (applications rate 454 g a.i./acre, once/crop cycle) does not indicate the potential for long-term dermal exposure.

5. Inhalation Exposure

The HIARC had previously established the endpoint for inhalation exposure (combined short- and intermediate-term) based on a chronic feeding/oncogenicity study in the rat. This study established a NOAEL of 0.23 mg/kg/day and a LOAEL of 2.3 mg/kg/day, which was based on clinical chemistry effects after 6-months of treatment (HED Doc. No. 014016 dated March 2,2000).

The registrant for diclofop-methyl contended that the exposure time (6-months) used to establish inhalation exposure endpoints is not consistent with the actual exposure scenario for diclofop-methyl which is approximately 90-days or less. Therefore, the HIARC re-evaluated the available data and selected the following endpoints for these risk assessments.

Short-Term Inhalation Exposure

Study Selected: Subchronic Feeding Study - Rat 870.3100, §82-1

MRID. Nos. 42573301

EXECUTIVE SUMMARY: In this subchronic toxicity study (42573301), Wistar rats (20/sex/dose) were fed diets containing diclofop methyl at concentrations of 0 (basal diet), 5, 20, 80, or 320 ppm (0, 0.34, 1.6, 6.3, or 26 mg/kg/day, males; 0, 0.44, 1.8, 7.1, 28 mg/kg/day, females) for 13 weeks, followed by a four-week, treatment-free (basal diet) recovery period with 10 rats/sex in the control, 80, and 320 ppm groups.

No treatment-related clinical signs or deaths occurred during the study. Males dosed at 320 ppm, had significantly ($p \leq 0.05$) decreased mean body weights (9-11%) and body weight gains (12 to 14%) at 46 and 92 days of treatment; body weights were decreased (8.4%, not significant) at 120 days. At the end of the recovery period, the body weights of high-dose males were still reduced (9%, not significant). The body weights of females were unaffected by treatment. Food consumption by high-dose males were decreased 4 to 14% (not significant) during the study. For the remaining treatment groups, food and water consumption were comparable to the control groups of both sexes.

Clinical pathology revealed treatment-related changes in some hematological and clinical chemistry parameters. Coagulation times and thromboplastin times were significantly decreased (19% and 31%, respectively) in high-dose males, but returned to control levels at the end of the recovery period. Clinical chemistry effects in 80 and 320 ppm males included decreases in cholesterol (29 and 45%, respectively) and total lipids (26 and 42%, respectively); free fatty acids were decreased in 80 ppm females (28%) and high-dose males (55%) and females (19%). In males, AST (SGOT) and ALT (SGPT) were increased at 320 ppm (20 and 30%, respectively); alkaline phosphatase was increased at 80 and 320 ppm in males (38 and 61%, respectively) and females (42 and 46%, respectively). At the end of the recovery period, only free fatty acid levels were still decreased at 80 and 320 ppm in males (26 and 23%, respectively) and females (24 and 20%, respectively).

Selected liver enzymes, used as indirect biomarkers for peroxisome proliferation and microsomal enzyme induction were measured at the ends of the main study and recovery period. Assay of liver homogenates showed increases in malic enzyme and catalase, both indirect enzyme markers for peroxisomal proliferation. Malic enzyme was significantly increased in 80 ppm and 320 ppm males (65 and 96%, respectively) and 320 ppm females (42%). Catalase was significantly increased in 5, 20, and 80 ppm females (85 to 189%) and in 320 ppm males (146%) and females (474%). Microsomal enzymes (glycerophosphate dehydrogenase, $NADPH_2$-dependent cytochrome c reductase and

glucuronyltransferase) were induced in 80 ppm females and/or 320 ppm males and females; ethylresorufin o-deethylase activity was decreased in 80 ppm males and 320 ppm males and females. At the end of the recovery period, there was no increase in enzyme activity associated with peroxisome proliferation; glucuronyltransferase activity was still increased in 80 and 320 ppm males and females.

Treatment-related pathological changes were limited to the liver. Absolute and relative liver weights were significantly increased in 80 and 320 ppm males and absolute liver weights, in 320 ppm females. Histopathological evaluations revealed centrilobular with marked cytoplasmic granulation (suggestive of peroxisome proliferation). Electron micrographs of the high-dose animals (1/sex) showed and increase is peroxisomes associated with an increase in smooth endoplasmic reticulum

The LOAEL was established at 80 ppm (6.3 mg/kg/day, males; 7.1 mg/kg/day, females) was based clinical chemistry effects (increased ALT, AST, ALP, malic enzyme and catalase; decreased cholesterol and free fatty acids) and centrilobular hypertrophy in the liver. The NOAEL was established at 20 ppm (1.6 mg/kg/day, males; 1.8 mg/kg/day, females).

The study is **ACCEPTABLE (GUIDELINE)** and fulfills the requirement for Subchronic 13 week toxicity study (82-1, 870.3100) the rat.

Dose and Endpoint for Risk Assessment: NOAEL = 1.6 mg/kg/day based on clinical chemistry findings (increased liver enzymes and catalase) and liver effects (increased absolute and relative liver weights, hypertrophy) at the LOAEL (6.3 mg/kg/day).

Comments about Study and Endpoint: The endpoint is considered appropriate since the effect (liver toxicity) is consistent with other studies in both rats and mice. This study is supported by the results of a chronic toxicity study in the rat which had significant decrease in body weight gain at 25 mg/kg/day after 93 days of treatment. A NOAEL was established at 2.3 mg/kg/day, which is similar to the NOAEL of the selected study. The Committee considered the developmental toxicity studies in the rat and rabbit to establish inhalation endpoints. The rat developmental study was not selected because the extrapolated NOAEL of 3 mg/kg/day [Maternal LOAEL of 10 mg/kg/day/3 (UF) for lack of NOAEL] is comparable to the dose of 1.6 mg/kg/day of the study selected for risk assessment, which was considered to be protective of rat developmental effects. The rabbit developmental toxicity study was not selected by the Committee because

1) The maternal NOAEL (0.3 mg/kg/day) is not consistent with the results seen in the studies with rats;

2) The NOAEL could be higher because of the wide spread in the doses tested (i.e. NOAEL = 0.3 mg/kg/day and the LOAEL of 3.0 mg/kg/day);

3) The dose (1.6 mg/kg/day) selected could be protective of the maternal effects seen in the rabbit; and

4) Higher confidence in the results seen in rats which showed the liver to be the organ of toxicity.

6. Intermediate-Term Inhalation Exposure

Study Selected: Subchronic Feeding Study - Rat 870.3100, §82-1

MRID. Nos. 42573301

EXECUTIVE SUMMARY: Short-term inhalation exposure

Dose and Endpoint for Risk Assessment: Short-term inhalation exposure

Comments about Study and Endpoint: Short-term inhalation exposure

7. Long-term Inhalation Exposure

Study Selected: None

MRID. Nos.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: The use pattern (applications rate 454 g a.i./acre, once/crop cycle) does not indicate the potential for long-terminhalation exposure.

D. Recommendation for Aggregate Exposure Risk Assessments

For acute aggregate exposure risk assessment, combine the high end exposure values from food + water and compare it to the acute RfD.

For short-term aggregate risk, the dermal and inhalation exposures can be combined due to a common toxicological endpoint (liver toxicity). However, these routes can NOT be combined with oral exposure, since developmental effects were identified for this route (oral).

Based on the use pattern, long-term aggregate exposure risk assessment is not required

For cancer risk assessment, the total dermal and inhalation exposure will be compared to the Q_1* of $2.3 * 10^{-1}$ $(mg/kg/day)^{-1}$.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

A. Carcinogenicity Studies

1. Combined Chronic Toxicity/Carcinogenicity Study - Rat 870.4300, §83-5

MRID No: 43927302

Executive Summary: In a chronic toxicity/oncogenicity study, diclofop-methyl was administered to a total of 80 Wistar rats/sex/dose in the diet at dose levels of 0, 4.5, 45, or 450 ppm (0, 0.23, 2.3, or 25 mg/kg body weight/day for males, and 0, 0.3, 3, or 32 mg/kg/day for females) for up to 2 years. Ten rats/sex/dose were sacrificed after 12 months. Twenty rats/sex/dose were treated in a 24-month toxicity study and 50 rats/sex/dose comprised a 24-month carcinogenicity study. Fifty additional female rats were administered the compound at 900 ppm (79 mg/kg body weight/day) for 24 weeks.

Dose levels up to 450 ppm did not increase mortality over controls. The 900 ppm dose was not tolerated by the females tested and this dose group was terminated after 24 weeks. At 45 ppm, males and females in the 24-month studies showed signs of liver toxicity, including increased liver weights, impaired lipid and protein metabolism, and increased liver enzyme activity. Related microscopic findings were hepatocellular hypertrophy, epithelial lipofuscin storage, and necrosis; the effects were more pronounced in males. Liver cell enlargement was observed in both sexes at 45 ppm in the 12-month study. Spleen weight was decreased at 450 ppm. Increases in kidney weight in males were significant and dose-related at 45 ppm. Also at 45 ppm, kidneys of both sexes exhibited a shift in lipofuscin storage from focal to diffuse. At the high dose of 450 ppm, body weight gain was significantly reduced in both sexes in the 12-month and two 24-month studies. In the 24-month studies, treatment-related increases in absolute and/or relative liver and kidney weights were observed at the high dose in males and females. The high dose caused significant decreases in red blood cell parameters, impaired lipid and protein metabolism, and increased liver enzyme activity, more so in males than in females. In addition to the microscopic liver abnormalities seen from the 45 ppm dose, the high dose produced a significant showing of atypical eosinophilic foci and basophilic foci in both sexes.

The LOAEL for systemic toxicity is 45 ppm in male (2.32 mg/kg/day) and female (3.05 mg/kg/day) rats, based on liver toxicity manifested as increased organ weight, impaired lipid and protein metabolism, increased enzyme activity, hepatocellular hypertrophy, and increased epithelial lipofuscin storage, and increased kidney weight and a shift from focal to diffuse lipofuscin storage pattern. The NOAEL is 4.5 ppm in males (0.23-0.27 mg/kg/day) and females (0.3 mg/kg/day). The low dose of 4.5 ppm was adequate to establish a NOAEL.

The high dose of 450 ppm was adequate to assess the chronic toxicity and carcinogenic potential of diclofop-methyl in male and female rats.

Under conditions of this study, diclofop-methyl induced liver tumors in males and females, adrenal gland and testicular tumors in males, and uterine and thyroid tumors in females at 450 ppm (25.2 - 29.3 mg/kg/day, males; 32.4 - 36.6 mg/kg/day, females). The incidence of combined hepatocellular adenomas and carcinomas in the two 24-month studies was 42.0% in males and 27.1% in females. Incidence of the carcinoma, detected in 26% of males and 20% of females was higher than for the adenoma, indicating malignancy. These liver neoplasms were also observed in females at 45 ppm. In addition at 450 ppm, females exhibited a significant 8% increase in incidence of thyroid follicular cell adenoma. Incidences of uterine glandular polyps (8%), testis Leydig cell tumors (26% versus 6 and 8% in concurrent and historical controls), and adrenal gland medullary adenomas (6%) in males, also showed significant trends, and were higher than the average historical controls for the performing laboratory.

This study is classified as **ACCEPTABLE (GUIDELINE)** and satisfies the guideline requirements 83-1 for a chronic toxicity study and 83-2 for a carcinogenicity study in the rat.

2. Carcinogenicity Study - Mouse 870.4200, §83-2(b)

MRID Nos: 92036058

Executive Summary: In this oncogenicity study, HOE NMRKf mice were fed diets at 0, 2.0, 6.3, or 20 ppm (0, 0.24, 0.76, 2.5 mg/kg/day, males; 0, 0.25, 0.77, 2.6 mg/kg/day, females) diclofop-methyl for 24 months.

No clinical signs of toxicity were observed during the study. Treatment-related mortality was increased in high-dose males (64.3% *vs*. 46.1%, control). Body weight and food and water consumption of treated mice were comparable to the concurrent control values for the entire study.

Clinical pathology did not reveal any treatment-related changes in any of the hematological or urinalysis parameters; clinical chemistry findings were observed. At the high-dose level, alkaline phosphatase activity was significantly increased in both sexes over the entire study. Males dosed at 6.3 ppm had elevated alkaline phosphatase activity through week 81, but not at study termination. High-dose males and females had significant increases in ALT (SGPT) activity and significant decreases in total glycerol.

Organ weights were significantly increased at both the interim and terminal sacrifices. At the interim sacrifice at week 88, the relative liver and kidney weights were increased in high-dose males and females; relative adrenal and brain weights were increased in high-dose females. At terminal sacrifice, the relative liver and kidney weights were increased in mid- and high-dose males and females; relative heart weights were increased in mid-dose males and high-dose males and females.

At necropsy, gross evaluations revealed swelling and discoloration in the livers, with more frequent findings in males. Histopathological examination revealed non-neoplastic lesions in the livers consisting of hepatocytic hypertrophy and eosinophilic inclusions. Electron micrographs revealed peroxisome proliferation in the livers of high-dose animals.

For high-dose males, hepatocellular tumor rates for adenomas and carcinomas were significantly increased (trend and pairwise) by 18% (20/113) and 14% (12/85), respectively; the combined tumor rate was 28% (32/113). The tumor rate of adenomas and carcinomas of the low-and mid-dose groups were comparable to control values.

The LOAEL for systemic toxicity was established at 6.3 ppm (0.76 mg/kg/day, males; 0.77 mg/kg/day, females) based on clinical chemistry findings (increased ALP) in males and increased relative organ weights in males (liver, kidney, heart) and females (liver, kidney), and hepatotoxicity (hypertrophy, eosinophilic inclusion, brown pigment deposits) in females. The NOAEL was established at 2 ppm (0.24 mg/kg/day, males; 0.25 mg/kg/day, females).

B. Cancer Classification

The Carcinogenicity Peer Review Committee met on February 10, 1993 to discuss and evaluate the weight-of evidence on diclofop-methyl with particular reference to its carcinogenic potential. The Committee agreed that diclofop-methyl should be classified as **Group C (possible human carcinogen)**. The Committee further recommended that for the purpose of risk characterization, a low-dose extrapolation model be applied to the experimental animal tumor data in the mouse. A **Q_1* of 2.3 x 10^{-1} (mg/kg/day)$^{-1}$** should be used for human risk assessment.

The Carcinogenicity Peer Review Committee is scheduled to meet on January 5, 2000 to discuss the combined chronic toxicity/carcinogenicity study in the rat.

IV. MUTAGENICITY

The data indicate that Diclofop-methyl is not mutagenic under the testing conditions and there is no mutagenic concern at the present time. The acceptable studies satisfy both the pre-1991 and new minimum initial mutagenicity testing requirements.

A. Gene Mutations

1. Bacterial reverse mutation test in *Salmonella typhimurim*

870.5100
MRID 00071904 (HED 000076)
Dose range: 0 to 5000 μg/mL +/- S9
Negative for mutagenic effects

Acceptable (Guideline)

2. *In vitro* mammalian cell gene mutation test with Chinese hamster V79 cells

870.5300
MRID 41573305 (HED 008541)
Dose range: 2 to 500 μg/mL +/- S9
Test was negative up to cytotoxic doses ($\geq$ 200 μg/mL, -S9; $\geq$ 300 μg/mL, +S9).
Acceptable (Guideline)

B. Cytogenetics

1. *In vitro* mammalian chromosomal aberration test in primary human lymphocytes

870.5375
MRID 41476004 (HED 013723)
Dose range: 1 to 500 μg/mL +/- S9
Test was negative up to a cytotoxic (500 μg/mL)
Acceptable (Guideline)

2. Dominant lethal test in male NMRI mice

870.5450
MRID 00071906 (HED 000076)
Dose range: 0, 10, 32, 100 mg/kg/day
Did not induce dominant lethal effects up to high dose tested
Acceptable (Guideline)

3. *In vivo* cytogenetic test in bone marrow cells of the Chinese hamster

870.5385
MRID 41737901 (HED 008850)
Dose range: 0, 200, 1000, and 2000 mg/kg
Chromosomal analysis did not show any treatment-related cytogenetic aberrations up to the highest dose tested
Acceptable (Guideline)

4. Mouse bone marrow micronucleus test

870.5395
MRID 00071905 (HED 000076)
Dose range: 0, 10, 32 and 100 mg/kg
Negative, no increase in incidence of polychromatic erythrocytes with micronuclei up to the highest dose tested.
Acceptable (Guideline)

C. Other Genotoxic Effects

1. Unscheduled DNA synthesis in primary rat hepatocytes *in vitro*

870.5550
MRID 00087816 (HED 001422)
Dose range: 0.5 to 50 μg/mL, cytotoxicity at 100 μg/mL
Did not induce significant increases in nuclear labeling of primary rat hepatocytes.
Acceptable (Guideline)

2. Unscheduled DNA synthesis in A549 human lung carcinoma *in vitro*

870.5550
MRID 41996902, 42437801 (HED 008796)
Dose range: 0.03 to 100 μg/mL ± S9
Did not induce significant increases in nuclear labeling human lung cancer cells up to the highest dose tested.
Acceptable (Guideline)

3. Mutagenic activity with *Saccharomyces cerevisiae*

870.5575
MRID: 00087820
Dose range: 0.25 - 1000 μg/kg
Negative for gene conversion
Acceptable (Guideline)

V. HAZARD-BASED FQPA CONSIDERATIONS

A. Neurotoxicity Data

No acute and subchronic neurotoxicity studies available. The existing studies did not indicate any neurotoxicity.

B. Developmental Toxicity

1. Developmental Toxicity in the Rat

EXECUTIVE SUMMARY: In a developmental toxicity study (92036042 and 42143402 historical control data), pregnant Wistar rats (20 to 25/dose) were dosed with diclofop-methyl (96%) at 0 (vehicle, sesame oil), 10, 32, or 100 mg/kg/day from gestation day (GD) 6 through 15.

Twelve of the 20 high-dose animals died between days 13 and 21 of pregnancy. Prior to death these animals were emaciated, had blood crusts on the nasal orifice, and were hypoactive. Remaining high-dose animals and those of the other treatment groups were not impaired. At terminal sacrifice, body weight of surviving high-dose dams was 20% lower than the control value; statistically significant, but biologically (5%), decreases in body weight were noted in the mid-dose group. At the low-, mid- and high-dose levels,

absolute liver weights were significantly increased (all greater than the historical control range) by 11.6%, 9.8%, and 23.1%, respectively, and relative liver weights, by 13%, 15%, and 48%, respectively. Because the liver is a target organ of toxicity, the effects on liver weights at the low-dose were considered treatment-related.

Due to the high mortality in the high-dose group, only 19 viable fetuses were available at terminal sacrifice. The number of live fetuses of the remaining low- (240) and mid- (194) were comparable to the control value (218). Fetal body weights were significantly decreased by 12.5% and 34% at the mid- and high-dose levels, respectively, and crown/rump lengths by 5.8% and 18% at the mid- and high-dose levels, respectively.

With the exception of the intercurrent deaths in the high-dose group, all gestation and caesarean section parameters of treated animals were all comparable to controls. Fetal examinations revealed four major malformations in four different litters: one in the control (anophthalmia) and three in the mid-dose group (one each microphthalmia, bent hind limb, and diaphragmatic hernia). External findings consisted of increased fetal (litter) percentage of small fetuses at the mid- [6.9% (33%)] and high- [100% (100%)] dose groups. Visceral and skeletal abnormalities were evaluated by necropsy and body cross section examinations. At necropsy, visceral abnormalities consisted of increased percentages of enlarged and blood-filled heart [60% (33%)] at the high-dose level. Body cross section examination included the above abnormalities and the addition of increased percentage of distended ureter in the mid- [7.6% (28%)] and high- [22 % (33%)] dose groups. Skeletal abnormalities for fetuses (litters) at the mid- and high-dose groups included fragmented thoracic centra [5.9% (27%) and 50% (100%), respectively], weakly/non-ossified sternebrae [69% (94%) and 100% (100%), respectively] and non-ossified 5th metacarpal [62% (94%) and 100% (100%), respectively]. Although the incidence of non-ossified 5th metacarpal was increased in the low-dose group, the value was within the historical control range. At the high-dose slight/non-ossified skull bones [100% (100%)], weakly/non-ossified sacral vertebrae [40% (67%)] and pelvic girdle [20% (67%)], and non-ossified 1st - 5th toes [60% (100%)] were also observed.

Based on the results of the study (increased absolute and relative liver weights), the LOAEL for maternal systemic toxicity was established at 10 mg/kg/day, the NOAEL was not established.

Based on the results of this study (significant decreases in fetal body weight and crown-rump length, distended ureters, and skeletal abnormalities), the LOAEL for developmental toxicity was established at 32 mg/kg/day, the NOAEL was established at 10 mg/kg/day.

This study is ACCEPTABLE-GUIDELINE, and satisfies requirements [870.3700, §83-3(a)] for a reproductive toxicity study in the rat.

2. <u>Developmental Toxicity in the Rabbit</u>

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 92036043), diclofop-methyl (97±2.0% a.i.) in sesame oil was administered by gavage to pregnant Himalayan rabbits at concentrations of 0, 0.03, 0.3, or 3.0 mg/kg/day on gestation days (GDs) 7 through 19. Does were sacrificed on GD 29.

Two does each from the 0.03 and 3.0 mg/kg groups and one doe from the 0.30 mg/kg group delivered prematurely from GDs 25-29. No premature deaths occurred and no treatment-related clinical signs were observed.

When compared to concurrent controls, no treatment-related changes were observed in body weights at any dose level. During treatment, non-statistically significant (NS) decreases in body weight gains were observed in high-dose does during GDs 7-14 (14.6 g vs 35.3 g, control) and GDs 14-20 (-60 g vs -8.3 g control). During the post-treatment period (GDs 20-29), body weight gains were increased (NS) in high-dose does (217 g) compared to controls (115 g). Overall (GDs 0 - 29), body weight gains for high-dose does were slightly increased (NS) in high-dose does (177 g) compared to controls (126 g). During the treatment period (GDs 7 - 20), decreases of 5 to 35% (NS) in relative (g/kg/day) food consumption in high-dose does; during the post-treatment period decreases (NS) of 10% were still observed.

At necropsy, significant increases ($p<0.05$) were observed in absolute liver (15%) and kidney weights (29%) when compared to concurrent controls. Cesarean section data did not show any changes in the number of implantations/doe, resorptions/doe, postimplantation losses, and percent male were similar between control and treated groups. No treatment-related changes were observed upon macroscopic examination of the does.

External, skeletal, and visceral fetal examinations did not reveal any treatment-related effects.

The maternal LOAEL is 3.0 mg/kg/day, based on significantly increased absolute liver and kidney weights, decreased body weight gain, and reduced food consumption.

The maternal NOAEL is 0.30 mg/kg/day.

No treatment-related developmental effects were noted at any dose level.

The developmental LOAEL was not established.
The developmental NOAEL is ≥ 3.0 mg/kg/day.

This developmental toxicity study is classified **acceptable (guideline)** and does satisfy the guideline requirements (§83-3[b]) for a developmental toxicity study in the rabbit.

C. Reproductive Toxicity in the Rat

EXECUTIVE SUMMARY: In this two-generation (one-litter/generation) reproduction study (42060501, 42560501) male and female rats [Crl:CD(SD)BR Sprague-Dawley] were continuously dosed with diclofop-methyl at dietary concentrations of 0, 10, 30, or 100 ppm (males: 0, 0.7, 2.1, 7.3 mg/kg/day; females: 0, 0.9, 2.5, 8.4 mg/kg/day) for two consecutive generations.

No treatment-related clinical signs or mortalities were observed. Significant changes in body weights, body weight gains, and food consumption were noted, the differences were considered to be incidental and not related to treatment.

Changes in organ weights were observed in mid- and high-dose males and females. Liver weights were increased across generations (adults and pups) in both males and females. F0 and F1 adults showed increased absolute and relative (males only) liver weights at the high-dose level; mid-dose F0 females also had increased absolute and relative liver weights. Liver weights of F1 pups were not affected by treatment, however, the absolute liver weights were increased in mid- and high-dose F2 pups. Kidney weights were increased in mid- and high-dose F1 adult males and high-dose F0 adults. Kidney weights were decreased in F1 (males only) and F2 pups at the high-dose level. F1 and F2 pups also had decreased spleen, adrenal and uterus weights; in F2 males, testes weights were also decreased.

Treatment-related histopathological effects were observed at the high-dose level in the liver, and, to a lesser degree, in the kidneys of both sexes and generations. Liver lesions (loss of intracytoplasmic irregular empty space and cellular hypertrophy and functional swelling of the nucleus of hepatocytes) were observed in a high percentage (> 68%) of F0 and F1 adults and F2 pups; increased incidence of foci of altered clear cells was observed in F1 adults (28 - 56%). The kidneys of high-dose animals showed yellow-brown intracytoplasmic pigment deposits in the convoluted tubule in F0 adults (44 - 56%), focal subacute to chronic interstitial nephritis in F1 adult males (52%), hyaline casts in F1 adults (24 - 72%) and calcified deposits in the medulla in F1 pups (> 48%).

At the high-dose level, effects included significant delays in developmental growth. Mean body weights were significantly lower for F0 pups (56%) on day 21 and F2 pups of days 1 (8%), 7 (13%) and 21 (21%). Physical development landmarks (pinna unfolding, incisor eruption, and eye opening) were delayed at the high-dose level, but were considered to be secondary to the decreased body weight. In the F0 generation, F1 litters, the mean number of live pups/litter was significantly deceased at the mid- and high-dose levels (11.0 and 10.3, respectively) on day 0, compared to the control value (12.3); on day 4 (precull), the number of live pups/litter was decreased at the high-dose level (9.1), compared to the control (11.8). Because the number of live pups/litter in treated animals in the F1 generation, F2 litters, were comparable to control values, the observed differences in the F1 litters were not considered to be treatment-related. The gestation length was significantly shorter in the high-dose, F1 litters (21.7 days *vs* 22.1 days for control), the value was within the historical control range.

Based on the results of the study (liver weight increases and histopathological lesions

in liver and kidney), the LOAEL for systemic toxicity was established at 30 ppm (2.1 mg/kg/day, males; 2.5 mg/kg/day, females), the NOAEL was established at 10 ppm (0.7 mg/kg/day, males; 0.9 mg/kg/day, females).

Based on the results of this study (reduced fetal body weights and delayed physical development), the LOAEL for reproductive toxicity was established at 100 ppm (7.3 mg/kg/day, males; 8.4 mg/kg/day, females), the NOAEL was established at 30 ppm (2.1 mg/kg/day, males; 2.5 mg/kg/day, females).

This study is **ACCEPTABLE-GUIDELINE**, and satisfies requirements [870.3700, §83-4] for a reproductive toxicity study in the rat.

D. Determination of Susceptibility

The data provided no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to diclofop-methyl. In the prenatal developmental toxicity studies in rats and rabbits on the diclofop-methyl, no effects in the offspring were observed at maternally toxic doses.

E. Recommendation for a Developmental Neurotoxicity Study

Neither the subchronic or chronic toxicity studies in mice, rats and dogs, the developmental toxicity studies in rats and rabbits, or the reproduction study in rats indicated that the nervous system was specifically affected by treatment with diclofop-methyl. Thus, there is no indication that diclofop-methyl is a neurotoxic herbicide.

There are no acute (§81-8, 870.6200a) and subchronic (§82-7, 870.6200b) neurotoxicity studies available (not required).

VI. DATA GAPS

There are no data gaps for the standard Subdivision F Guideline requirements for a food-use chemical by 40 CFR Part 158.

VII. HAZARD CHARACTERIZATION

Diclofop-methyl [2-(4-(2',4'-dichlorophenoxy)phenoxy)propionic acid, methyl ester] is the active ingredient of Hoelon, which is currently registered as a herbicide for use on food crops (wheat, barley) and golf course turf. Hoelon 3EC is currently the only registered end-use product. Toxicological data for diclofop-methyl are available, complete, and acceptable. Diclofop-methyl is moderately toxic by oral or dermal exposure (toxicity category II), but less so by inhalation (toxicity category IV). In the primary irritation studies, Diclofop-methyl produced slight ocular irritation (toxicity category III) and slight dermal irritation (toxicity category IV).

Subchronic feeding and dermal toxicity studies in the mouse and/or rat, the chronic

toxicity/oncogenicity studies in the rat and mouse, and the two generation reproduction study in the rat all identified the liver as the target organ for toxicity. Liver weights were increased in treated animals in all of these studies. In the two-generation study increased liver weights were observed across generations in both sexes; in some cases pup liver weights were also affected. Histological examination of the livers revealed an increased incidence hepatic lesions following subchronic oral and dermal exposure and multi-generational exposure; the carcinogenicity studies in the rat and mouse showed increased incidence of adenomas and carcinomas.

Even though diclofop-methyl is carcinogenic in rats and mice, the mutagenicity studies were all negative.

There is growing evidence that the observed hepatic carcinogenicity in the rat and mouse is a result of peroxisome proliferation. Most other pesticides in the same chemical class (diphenyl ethers) as diclofop-methyl are also carcinogenic and also produce peroxisome proliferation. Although detailed mechanistic studies have not been carried out with diclofop-methyl, the subchronic toxicity studies in the rat and mouse included measurement of enzyme activities used as indirect markers for peroxisome proliferation. In these studies, malic enzyme and catalase were markedly increased during treatment, but returned to control levels after treatment-free period. In the chronic toxicity study, electron micrographs showed an increase in the number of peroxisomes in the livers of treated rats.

Based on hepatotoxicity in the mouse carcinogenicity study, the Cancer Assessment Review Committee (CARC) classified diclofop-methyl as a Group C carcinogen (possible human carcinogen) with a Q_1* of 2.3×10^{-1} $(mg/kg/day)^{-1}$. The CARC is scheduled to evaluate the acceptable carcinogenicity study in the rat.

VIII. ACUTE TOXICITY

Acute Toxicity of Diclofop-methyl, Technical

Study Type	Animal	Results	Tox Cat	MRID No
81-1: Acute Oral (LD_{50})	Rat	Male: 481 mg/kg Female: 500-630 (estimate) mg/kg Combined 512 (428-636) mg/kg	II	41476001 92036052
		Male: 580 mg/kg	II	00123982
		Female: 557 mg/kg	II	00123983
81-2: Acute Dermal (LD_{50})	Rat	Male and Female: > 2000 mg/kg	II	00071522 92036013
81-3: Acute Inhalation (LC_{50})	Rat	Male and female > 3.83 mg/L	IV	00032595
		Male and female > 4.75 mg/L	IV	41573304
		Male and female > 3.83 mg/L	IV	00032595
81-4: Primary Eye Irritation	Rabbit	Slight ocular irritant, Conjunctival redness and discharge at 24 hr, cleared by 72hr	III	42428601
81-5: Primary Dermal Irritation	Rabbit	Slight irritant, PII = 0.8 (0 to 72 hr)	IV	40213506
81-6: Dermal Sensitization	Guinea Pig	Buehler: Negative	NA	41476003 92036047
		Maximization: Moderate to severe sensitizer	NA	41476002 41476003 92036046

IX. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected and Margins of Exposures for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary (Females 13 - 50)	NOAEL = 10 mg/kg/day	Decreased fetal body wts, distended ureters, skeletal abnormalities. These effects could be attributed to a single dose.	870.3700 Developmental toxicity study in the rat
	UF = 100	Acute RfD = 0.1 mg/kg/day	
Acute Dietary (General Population including Infants and Children)	None	No endpoint selected	None
Chronic Dietary (Non-cancer)	NOAEL = 0.23 mg/kg/day	Based on increased relative liver and kidney wts, liver enzymes, liver histopathology (hypertrophy, lipofuscin storage). Effects and NOAEL consistent with other studies in mouse and dog.	870.4300 Chronic toxicity study in the rat
	UF = 100	Chronic RfD = 0.0023 mg/kg/day	
Short-Term (Dermal)	NOAEL = 5 mg/kg/day	Based on increased liver enzymes, proteins, and absolute and relative liver weights.	870.3200 21-Day Dermal Toxicity Study in the Rat
Intermediate Term (Dermal)	NOAEL = 5 mg/kg/day	Based on increased liver enzymes, proteins, and absolute and relative liver weights.	870.3200 21-Day Dermal Toxicity Study in the Rat
Long-term Non-cancer (Dermal)	Based on the use pattern (applied at the rate of 454 g ai/acre up to a maximum of one application/crop cycle), this risk assessment is not required		
Inhalation (Short and Intermediate-Term	NOAEL = 1.6 mg/kg/day	Based on increased liver enzymes, proteins, and absolute and relative liver weights.	870.3100 Subchronic Oral Toxicity Study in the Rat
Inhalation (Long-term)	Based on the use pattern (applied at the rate of 454 g ai/acre up to a maximum of 1 application/crop cycle), this risk assessment is not required		
Cancer (Dermal and Inhalation)	Q_1* of 2.3×10^{-1} $(mg/kg/day)^{-1}$	Based on liver adenomas and carcinomas with significant trend and pair-wise comparisons.	870.4200 Mouse Carcinogenicity Study